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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/269,321	09/13/1999	WILLIAM KAELIN JR.	46793	9798

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EXAMINER	
SANDALS, WILLIAM O	

ART UNIT	PAPER NUMBER
1636	19

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/269,321	Fine et al.
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 26, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *15-27* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *15-27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Arguments

1. Arguments presented in Paper No. 18, filed August 26, 2002 have overcome the rejection of the claims under 35 USC 112, first paragraph in the previous office action, and the rejection is withdrawn.

2. Arguments presented in Paper No. 18 have overcome the rejections of the claims under 35 USC 102 in the previous office action, and the rejections are withdrawn.

3. Arguments presented in Paper No. 18 have overcome the rejections of the claims under 35 USC 103 in the previous office action, and the rejections are withdrawn.

4. New grounds for rejection are presented below.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 15-23 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/18992 (McCormick of record) in view of Raj et al. (of record).

The claims are drawn to a method of selectively expressing a gene in a malignant cell (of a solid tumor/glioma) with a viral vector (adenovirus or herpes virus) which comprises an E2F responsive promoter element (DHFR, Pol alpha, BMyb, cMyc or E2F1) which controls expression of a (structural) gene (a positive or negative potentiator) which may be a TK gene, a cytotoxin (a suicide gene) or a cytokine. The E2F present in the malignant cell selectively induces expression of the gene.

McCormick (see especially pages 4, 5 and 27) taught the desirable and advantageous use of an adenoviral vector for the expression of structural genes such as the TK gene or suicide genes in a malignant cell using an E2F responsive promoter. McCormick did not discuss the details of determining the E2F levels in the malignant cell.

McCormick did not teach the use of an E2F responsive promoter to control expression of a gene in a glioma, nor that DHFR, Pol alpha, BMyb or cMyc responsive promoters were E2F responsive promoters.

Raj et al. taught (see especially the abstract and introduction) the use of an E2F responsive promoter (DHFR, Pol alpha, BMyb, cMyc or E2F1) to control expression of a structural gene in a glioma. Raj et al. discuss the details of determining the E2F levels in the malignant cell.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the teachings of McCormick with Raj et al. because each of McCormick and Raj et al. made obvious the use of an E2F responsive promoter to control the

expression of a structural gene in a malignant cell. Raj et al. taught the obvious, well known and equivalent use of E2F responsive promoters from DHFR, Pol alpha, BMyb, cMyc or E2F1. Raj et al. taught that the E2F responsive promoter was particularly useful in controlling the expression of a gene in a glioma cell. McCormick taught the desirable and useful transduction and subsequent expression of a structural gene under the control of an E2F responsive promoter in a malignant cell with an adenoviral vector.

One of ordinary skill in the art would have been motivated to combine the teachings of McCormick with Raj et al. because Raj et al. taught that an E2F responsive promoter was particularly useful in a method of expressing a desired gene in a glial cell tumor where the E2F levels are determined in the malignant cell. McCormick taught that adenoviral and herpes viral vectors were particularly useful in expression of genes such as the TK cytotoxic gene for diagnosis and therapy of neoplastic diseases in a selective method of expression using an E2F responsive promoter in a malignant cell. The use of the E2F responsive promoter is made obvious because both of McCormick et al. and Raj et al. use E2F to control the expression of a gene in a malignant cell. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of McCormick with Raj et al.

7. Claims 15-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick with Raj et al. as applied to claims 15-23 and 25-27 above, and further in view of US 6,310,045 (Barber et al.).

The claims are drawn to the invention as described above and also where the cytotoxin is *Pseudomonas* exotoxin A.

McCormick and Raj et al. taught the invention as described above.

McCormick and Raj et al. did not teach that the cytotoxin was *Pseudomonas* exotoxin A.

Barber et al. taught (see especially the summary and columns 5-7 and 10) cytotoxins such as *Pseudomonas* exotoxin A which are well known and are used in methods of expression of an adenoviral or herpes viral vector in a malignant cell. Barber et al. taught that the *Pseudomonas* exotoxin A was well known and equivalent to the TK gene of McCormick et al. for use as a cytotoxin in a viral vector for killing malignant cells.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the teachings of McCormick with Raj et al. with Barber et al. because each of McCormick and Raj et al. made obvious the use of an E2F responsive promoter with selective activity which controlled the expression of a structural gene in a malignant cell. McCormick and Barber et al. taught the use of a well known cytotoxin such as TK to kill a malignant cell. Barber et al. taught the obvious and equivalent use of the cytotoxins TK and *Pseudomonas* exotoxin A in a method of expression of the cytotoxins TK or *Pseudomonas* exotoxin A in a tumor cell from an adenoviral or herpes viral vector.

One of ordinary skill in the art would have been motivated to combine the teachings of McCormick with Raj et al. and Barber et al. because each of McCormick and Raj et al. taught the desirable and beneficial use of an E2F responsive promoter to confer selective activity to control the expression of a structural gene in a malignant cell. Barber et al. and McCormick each describe the desirable and advantageous use of adenoviral or herpes viral vectors to selectively transduce and express a cytotoxin in a malignant cell. McCormick and Barber et al. taught the desirable and beneficial use of a well known cytotoxin such as TK to kill malignant tumor cells. Barber et al. taught the obvious and equivalent use of TK or *Pseudomonas* exotoxin A in a method of expression of the cytotoxin TK or *Pseudomonas* exotoxin A in a tumor cell from an adenoviral or herpes viral vector. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of McCormick, Raj et al. and Barber et al.

Conclusion

8. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can

be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the William Phillips, whose telephone number is (703) 305-3482.

William Sandals, Ph.D.
Examiner
November 15, 2002

TERRY MCKELVEY
PRIMARY EXAMINER